**Review**

# Designs of drug-combination phase I trials in oncology: a systematic review of the literature

M-K. Riviere,[1,2] C. Le Tourneau,[3,4] X. Paoletti,[3] F. Dubois,[2] S. Zohar[1]

1: INSERM, U1138, Team 22, Centre de Recherche des Cordeliers, Université Paris 5, Université Paris 6, Paris, France;

2: IRIS (Institut de Recherches Internationales Servier), Suresnes, France;

3: Institut Curie INSERM, U900, Paris, France ;

4: Department of Medical Oncology, Institut Curie, Paris, France

**Corresponding author:** Ms Marie-Karelle Riviere

INSERM UMRS 1138, Team 22, Centre de Recherche des Cordeliers

Escalier D, 1er étage

15, rue de l'Ecole de Médecine

75006 Paris, France

Tel: +33-1-4427-7676

Email: marie-karelle.riviere@crc.jussieu.fr

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**Abstract**

**BACKGROUND**

Combining several anticancer agents can increase the overall anti-tumor action, but at the same time, it can also increase the overall observed toxicity. Adaptive dose-escalation designs for drug combinations have recently emerged as an attractive alternative to algorithm-based designs, and they seem more effective in combination recommendations. These methods are not used in practice currently. Our aim is to describe international scientific practices in the setting of phase I drug combinations in oncology.

**MATERIAL AND METHODS**

A bibliometric study on phase I dose-finding combination trials was conducted using the MEDLINE® PubMed database between January 1, 2011 and December 31, 2013. Sorting by abstract, we selected all papers involving a minimum of two-agents and then retained only those in which at least two agents were dose-escalated.

**RESULTS**

Among the 847 references retrieved, 162 papers reported drug-combination phase I trials in which at least two agents were dose-escalated. In 88% of trials, a traditional or modified 3+3 dose escalation design was used. All except one trial used a design developed for single-agent evaluation. Our study suggests that drug-combination phase I trials in oncology are very safe, as revealed by the calculated median DLT rate of 6% at the recommended dose, which is far below the target rate in these trials (33%).

We also examined requirements of phase I clinical trials in oncology with drug combinations and the potential advantages of novel approaches in early phases.

**CONCLUSION**

Efforts to promote novel and innovative approaches among statisticians and clinicians appear valuable. Adaptive designs have an important role to play in early phase development.

**Keywords:** Drug combinations, Phase I trials, Dose-finding

## Introduction

Phase I trials in oncology are dose-finding studies that seek to determine the dose to recommend for further evaluation (recommended phase II dose [RP2D]). These trials are designed to obtain reliable information on the safety, pharmacokinetics, and mechanism of action of a drug. In oncology, dose-finding studies focus on determining the highest dose of a new drug with acceptable toxicity [1-2]. They are subject to the ethical constraint of minimizing the number of subjects treated at unacceptable toxic dose levels. Toxicity is measured as a binary endpoint, denoted as “dose limiting toxicity” (DLT), mainly using National Cancer Institute Common Toxicity Criteria. Most dose-escalation methods were developed for cytotoxic agents with the assumption that toxicity increases with dose in a monotonic fashion. Therefore, the RP2D has traditionally been the highest safe dose, called the “maximum tolerated dose” (MTD). These methods were specifically designed for the evaluation of single agents. In clinical practice, the traditional “3+3” dose escalation design or a modification thereof are the most frequently used dose-escalation methods in phase I trials [3].

Drug combinations have been introduced with the goal of improving treatment efficacy by increasing overall anti-tumor activity and, presumably, survival. Successful drug combinations include a combination of cytotoxic agents for the treatment of germ-cell tumors and lymphoma, polychemotherapy for the treatment of germ-cell tumors [4-5], combinations of trastuzumab with a taxane for HER2-positive breast cancer [6], and a combination of BRAF and MEK inhibitors [7]. Although it can reasonably be assumed that toxicity increases with dose for a single drug, the determination of the relationship between toxicity and doses of multiple drugs remains elusive. When combining two or more agents, there may be a potential

synergistic effect, not only in terms of efficacy, but also in terms of toxicity [8]. Therefore, when combining several agents, the ordering between combinations according to their DLT rates is important. However, only partial ordering of DLT rates can be anticipated when the dose of only one drug is being escalated, whereas the dose of the other drugs in the combination is kept fixed (Figure 1). That is, referring to Figure 1a, in a row (or column), one agent is fixed while the other is increased. In this case, the DLT rates are increased with the dose of the agent. All these order relations in rows and columns (shown with the symbol inferior "<") lead to "a partial ordering of DLT rates" given in Figure 1a. For example, if 2 agents with 3 dose levels are considered, when a monotonic and increasing relationship is assumed with respect to both agents then a partial toxicity order is known between the 9 combinations. The lowest combination is dose level 1 of agent 1 combined to dose level 1 of agent 2 (1,1) and the highest combination is dose level 3 of agent 3 combined with dose level 3 of agent 2 (3,3). Presumably, combination (1,2) is less toxic than (2,2), which is also presumably less toxic than (3,2), etc. However, on a diagonal, when the dose of one agent is increased while the dose of the other is decreased, it is not known which combination is more toxic. For instance, is the (1,2) combination more or less toxic than the (2,1) combination? Therefore, several toxicity orderings between combinations are possible (two examples are given in Figures 1b and 1c).

In practice, drug-combination phase I trials raise several challenging points to be defined prior to the trial onset [9-17]: 1) starting dose of each agent; 2) choice of the dose range of each agent and the number of combinations to be evaluated; and 3) total sample size that is strongly related to the number of possible combinations. In this study, we aimed at evaluating how drug-combination phase I trials in oncology

have been designed in the last three years and what the principal investigator's choices were with regard to the dose range, number of combinations, and statistical design.

**Material and methods**

All drug-combination phase I trials published between January 1, 2011 and December 31, 2013 were reviewed (Figure 2). We restricted our review to phase I combination trials where at least two drugs were planned to undergo dose escalation. Trials involving radiation therapy or drugs other than cytotoxic agents and molecularly targeted agents (MTAs) were excluded. MTAs were defined in our review as anticancer agents that selectively target molecular pathways, as opposed to DNA, tubulin or cell division machinery. Hormonal therapy and biological therapeutics, such as immunotherapy, were included.

We performed a MEDLINE® PubMed search using the following terms: "*Clinical Trial, Phase I[ptyp] AND cancer[MeSH] AND "2011/01/01"[PDAT] : "2013/12/31"[PDAT AND (combination OR combine OR combined OR combining)*". Among 847 references retrieved, 162 papers reported on a drug combination phase I trial meeting our inclusion criteria, 381 papers involved drug combinations where only one agent was dose-escalated, while the others were fixed (Figure 2).

The following data were recorded: the number of drugs undergoing dose escalation, the types of drugs (cytotoxic agent versus MTA), the number of dose levels planned for each drug, justification of the starting doses, number, choice and justification of drug combinations, dose-escalation design used, addition of drug combinations during the trial, number of patients included, and target toxicity level. We also performed a quality control analysis of the reviewed papers.

In this review, the lowest combination is defined as the combination corresponding to the lowest dose levels planned of each agent. A monotonic and increasing dose-toxicity relationship with respect to both agents signifies that when fixing one agent or the other to a certain dose independently, the DLT rate of the combination increases with the dose level of the remaining agent.

## Results

### *Characteristics of the drugs*

The 162 phase I trials involved 340 drugs that underwent dose escalation. In the majority of the trials, only 2 drugs underwent dose escalation (Table 1). Trials that involved only cytotoxic agents, only MTAs, and a combination of cytotoxic agents and MTAs were roughly equally distributed.

### *Dose levels*

The median number of patients included per trial was 25 [range: 7-136] (Table 1). In 69% of cases, the starting combination in the trial was the one associated with the lowest dose level of each agent considered in the trial. The starting dose used in the trial was justified (short explanation or only references) in 35% of the trials, respectively (Figure 3). The dose levels of each agent involved in the combinations of the clinical trial were justified in only 47 publications (29%). Results of a quality control analysis are provided in Figure 3.

### *Dose combinations*

The median number of planned combinations in the trial protocol was 5 [range: 2-16], 5.5 [range: 3-15] and 12 [range: 12-12] in trials combining two, three, and four drugs,

respectively. The median number of actually evaluated combinations was 4 [range: 2-12], 4 [range: 2-9] and 3 [range: 3-3] in trials combining two, three, and four drugs, respectively.

The median ratio of the number of planned combinations to the number of possible combinations (defined as the number of planned combinations divided by product of the number of doses levels of each agent) was 0.67 [range: 0.25-1], 0.24 [range: 0.17-0.63] and 0.13 [range: 0.13-0.13] in trials combining two, three, and four drugs, respectively.

***Dose escalation method***

In most trials, a traditional 3+3 or a modified 3+3 dose escalation design was used (Table 1). Only one trial used a design developed for combination trials. Most of the selected papers assumed a monotonic and increasing dose-toxicity relationship, in 62% of trials, whereas 38% of papers assumed only a partial monotonic and increasing dose-toxicity relationship.

In 24% of the trials, additional drug combinations were evaluated during the trial for safety reasons.

***Safety***

The DLT target rate associated with the recommended dose was 33% in most studies (Table 1). However, according to the number of patients and DLTs reported at the RP2D, the calculated median DLT rate at the recommended dose was 6% [range: 0%-40%]. Nevertheless, in only 4% of trials was the DTL rate estimated by the authors at the recommended combination for further studies.

In 3% of the studies, the trial was stopped at the first dose level due to DLTs. Five trials were stopped for reasons relating to over-toxicity; that is, the lowest combination evaluated in the trial was considered too toxic and the trial was abruptly halted without finding a tolerable combination. Fifty-six per cent of the trials found the MTD according to its initial definition, and 11% of trials found an MTD without observing any DLTs throughout the trial. In 48% of trials, the progress observed in the trial did not match the initial planned method. The trials that did not match the intended plan were all 3+3 or modified 3+3 statistical designs. The main observed differences from planning were: (1) difference in the planned number of patients per cohort with no justification and (2) a different allocation rule during the trial.

**Discussion**

Our study suggests that drug-combination phase I trials in oncology are safe. Overall, however, the starting doses of the drugs in the trials reviewed, as well as the dose levels and the dose-escalation steps, were barely justified. In addition, the dose levels explored in the drug-combination phase I trials included in our study did not reflect the entire space of possible drug combinations. In most of cases, dose levels seemed to be arbitrarily decided. It remains to be evaluated whether non-explored drug combinations would have been able to produce increased anti-tumor activity without jeopardizing patient safety.

Only a limited number of combinations were explored and only a sub-set of combinations was evaluated, despite the larger number of possible combinations. In our MEDLINE® PubMed search, the median ratio of the number of combinations considered to the number of possible combinations indicated that approximately one-third of the combinations were not considered for two-drug combinations. This

indicates that trial investigators may have selected the combinations to be evaluated prior to the trial, and that some combinations were excluded without documented rationale. Exploring the entire combination space is obviously not feasible in practice. Nevertheless, the choice of the combinations to explore should not be limited by partial toxicity ordering. The design should have the possibility to explore any combination estimated to be the best. In fact, due to possible interactions between drugs, pre-selecting an arbitrary reduced sub-set of combinations induces a risk in selecting a combination with a DLT rate far from target toxicity. Even if the targeted DLT proportion was most often about 33% in the papers, the median DLT rate associated with the RP2D at the end of the trial was much lower. That could be a reason why an intermediate combination was added, in some cases, which induced a non-monotonic dose-toxicity relationship in some trials.

During the review of this paper, the question was raised whether the low DLT rate could be due to MTAs for which the toxicity profile is different. Indeed, for these non-cytotoxic agents, very low toxicities are often observed with sometimes cumulative low-grade toxicities that may become dose limiting. The cumulative low-grade toxicities partially explain deviance from the intended plan. An FDA guideline [18] reported: "…cancer vaccine trials have used the "3 + 3 design" and the results show that, except in very rare situations, an MTD for a cancer vaccine may not be identified. In these trials, the dose-toxicity curve may be so flat that the highest dose that can be administered is limited by manufacturing or anatomic issues rather than toxicity. Therefore, this "3+3 design" may not be the most suitable approach to gathering information from early phase trials of cancer vaccines, and alternative trial designs should be considered." They added that: "When no DLT is expected or

achieved, optimization of other outcomes, such as the immune response, can be useful to identify doses for subsequent studies".

For this reason, standard dose-finding designs dealing only with toxicity, such as the "3+3" do not seem appropriate for some biological agents [19]. First, it is true that the dose determination based on less than 33% DLT on the first cycle of treatment for molecularly targeted agents is problematic. These non-cytotoxic agents have different toxicity profiles than cytotoxic agents. One possible reason for the observed low DLT rate at the RP2D could be due to the DLT evaluation only on the first cycle of treatment. Physicians can observe no DLT on the first cycle but cumulative low-grade toxicities that become dose limiting with later cycles of treatment. For this reason, they decrease the recommended dose level for phase II (in contrast to the statistical design), rendering a low DLT rate (evaluated only on the first cycle) for this dose. All cumulative toxicity grades on all available cycles should be considered in the statistical analysis for dose recommendations. Furthermore, depending on the biological agent, several dose-efficacy relationships could be observed: (1) monotonic and increasing; (2) monotonic increasing and then reaching a plateau; and (3) monotonic increasing and then decreasing with the dose. In the latter two cases, only studying toxicity in the dose-finding process is not sufficient, and efficacy should also be considered. Therefore, alternative designs should be developed. Adapting the way of doing early phase clinical trials for these innovative molecules is important, but changing usual practices in oncology is very complex and difficult. If regulatory agencies were to give clear instructions, trial sponsors and investigators would need to apply them. There are published statistical designs proposing alternative methods [20-22], therefore statistics should not be a limited factor.

However, in calculating the median DLT rate for trials in which the combination involved cytotoxic agents, we observed a DLT rate of 4%. Therefore, we do not believe that this is due to the type of agent but rather to the use of the “3+3” algorithm, where the dose retained is the dose under 2 DLTs over 3 or 6 patients. Indeed, in the trials studied, either the combination level was associated with no (or very few) DLTs, or the highest dose level in the trial did not even reach the target toxicity. Thus, due to the small number of patients (3 or 6) with the “3+3” design, the estimation is unreliable and often close to 0%. It should be noted that combination trials of MTAs included more patients at the RP2D than combination trials of cytotoxic agents, perhaps due to the uncertainty on overall toxicity discussed above. That could explain the small increased difference in DLT rates despite the toxicity profile of MTAs, as the estimation with a greater number of patients is more reliable.

Most of the drug-combination phase I trial designs used the traditional “3+3” design or a modified version. Recent dose-escalation designs have been developed for drug combinations but never employed in the trials reviewed [23-30]. In all but one trial reviewed, the dose-toxicity relationship was considered to be one-dimensional, whereas the reality involved several agents inducing a multi-dimensional issue. Most of the time, the problem was brought back into a one-dimensional space by pre-selecting combinations with a known toxicity order to be evaluated.

The methods for single agents do not always seem appropriate for combination phase I trials in which the doses of several drugs vary, as they are not designed to take a multi-dimensional space into account. Several alternative designs were proposed for either algorithm-based or design-based combinations that give the possibility to explore any appropriate combination in the entire combination space according to the accumulated data. Ivanova and Wang proposed an “up-and-down

algorithm-type" method with isotonic regression [31] that was used recently in Gandhi et al. [32]. Conaway et al. developed a design for multiple agents based on partial orders [33] that was used in the publications reviewed in Jones et al. [34]. Other authors have proposed model-based designs in which the multi-dimensional feature of the entire combination space is taken into account. These methods allow considering the entire combination space that includes a large number of combinations with non-monotonic relationships. It should be noted that these methods do not permit exploring combinations that are estimated to be too toxic. In a recent comparison, based on simulations, Riviere et al showed that these designs were comparable and had high operational characteristics [30]. However, it is true that these designs have only been shown to be effective in simulation studies (Riviere et al, Stat Med 2014), and they require the involvement of a statistical expert.

In a recent editorial, Mandrekar [9] pointed out the importance of using adequate methods for the evaluation of combinations. Our bibliometric work supports this editorial with a large and detailed study on clinical practice in the phase I settings for combination trials.

Our analysis did not include trials published in abstract form. Although this induces a selection bias, the present analysis still provides useful data that may help improve the design of drug-combination phase I trials.

In our review, we did not stated that both agents must be administered at their single-agent MTD when in combination. As two agents can have a synergistic, antagonistic or independent effect on toxicity, the question of achieving doses (for each agent) that nearly approximate the recommended phase II dose is up for debate. It is a strong assumption that the addition of both agents at their MTD would result in the same toxicity as if administered alone. We believe that considering all

combinations of dose levels between the two agents as a possible MTD should be acceptable, under medical restrictions and prior knowledge of such combinations. The recommended combination at the end of the trial should not be limited to the combination of both single-agent MTDs, but the dose-finding process should be performed similarly to that of a single-agent in order to recommend the combination with a toxicity rate closest to or below a pre-defined target. Indeed, in the same way, combining two agents can also induce a synergistic, antagonistic, or independent effect on overall efficacy. This point should be discussed for each combination of drugs, as the mechanism of action of each agent can differ.

In conclusion, we believe that the design of drug-combination phase I trials in oncology can be improved. We recommend that the starting doses of the drugs, as well as the dose levels and the dose-escalation steps, need to be appropriately justified. These parameters should be determined with the aim to: 1) ensure patient safety; 2) treat as few patients as possible at presumably infra-therapeutic doses; and 3) identify the optimal drug combination for further evaluation. We strongly support the use of innovative designs that are able, at least in theory, to fulfil these requirements.

**Figure legends**

**Figure 1.**

**(a) Partial known ordering between combinations. (b) Possible orderings between combinations according to increasing DLT rates.**

**Figure 2.**

**Flow chart of the publications found from the MEDLINE® PubMed search.**

**Figure 3.**

**Control quality of 162 trials reviewed.**

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